RESEARCHPROJECT

TREATMENT OF DEPRESSION IN THE ELDERLY WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) USING THETA-BURST STIMULATION (TBS): RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED,CLINICAL TRIAL

PRINCIPAL INVESTIGATOR

Leandro da Costa Lane Valiengo

RESPONSIBLE INVESTIGATOR

André Russowsky Brunoni, Orestes Vicente Forlenza, Wagner Farid Gattaz, Bianca Silva Pinto, Bruna Bariani Teixeira, Cristiane Siqueira Miranda, Henriette Baena Cardeal, Julia Cunha Loureiro, Kalian Almeida Pereira Marinho, Leonardo Afonso dos Santos, Luara Cristina Tort, Rafael Garcia Benatti, Renata Aparecida Rocha Vaughan, Roberta de Arruda Mendes Pereira Fiuza Dini Mattar, Paulo Jeng Chian Suen, Pedro Subrack Oliveira and Valquíria Aparecida da Silva.

INSTITUTIONS: Laboratório de Neurociências (LIM-27) Instituto de Psiquiatria –Hospital dasClínicas Faculdade de Medicina da Universidade de São Paulo São Paulo, SP, Brasil 2021

CLINICS HOSPITAL OF THE SÃO PAULO UNIVERSITY FACULTY OF MEDICINE- HCFMUSP

CONSENT FORM

PROJECT INFORMATION

Project title - TREATMENT OF DEPRESSION IN ELDERLY PEOPLE WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION BY THE THETA BURST METHOD: CLINICAL, RANDOMIZED, DOUBLE-BLIND TRIAL

Principal researcher - Orestes Vicente Forlenza

Department/Institute - Department and Institute of Psychiatry – IPq HCFMUSP

We invite you to participate, as a volunteer, in the research project "TREATMENT OF DEPRESSION IN ELDERLY WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION BY THE THETA BURST METHOD: CLINICAL, RANDOMIZED, DOUBLE-BLIND METHOD", responsibility of PROF researchers. DR. ORESTES VICENTE FORLENZA, to assess the efficacy of rTMS by the theta-burst method in the treatment of major depressive disorder in the elderly.

Read carefully what follows and ask me about any questions you have. After being clarified on the following information, if you accept to be part of the study, sign at the end of this document, which is in two copies. One way belongs to you and the other to the responsible researcher. In case of refusal you will not suffer any penalty.

I declare that I have been clarified on the following points:

1 – This information is being provided for your voluntary participation in this study, which aims to treat depression in elderly patients.

2 – Procedures that will be used and purposes, including identification of procedures that are experimental: If you decide to participate, a history and clinical evaluation form (psychiatric and cognitive) must be completed and the following procedures will be performed:

- Transcranial magnetic stimulation;
- Collection of 10-40 mL (equivalent to 3 tablespoons) of blood by peripheral puncture of the forearm vein;
- Collection of 12-15mL (equivalent to 1 tablespoon) of cerebrospinal fluid (CSF) or cerebrospinal fluid, in the morning, by puncture in the lumbar spine at the level of the space between the third and fourth lumbar vertebrae with a fine needle.

Blood and CSF samples will be used for biochemical and genetic determinations. All material will be encoded so that the identity of the participants is not revealed.

- Neuropsychological Assessment;
- MCD Assessment;

We will perform a complete battery of the quantitative sensitivity test and four different techniques of Diffuse Inhibitory Control of pain. The quantitative sensitivity test is composed by the tests of the mechanical detection threshold, the pain threshold, for this purpose von Frey filaments from 1.7 to 300 g will be used. The test also consists of an assessment of thermal sensitivity. And for the detection of the thermal threshold of heat and cold, we will use the limit methods. As an example, the contact thermode (30x30 mm) of Peltier elements will be placed over the test areas at a basal temperature of 32ºC. The temperature will be increased or reduced by 1ºC per second to a temperature of up to 50ºC (LTC) or 0ºC (LTF). The tests will be performed on the right and left hands and on the surface of the right and leftthigh of the volunteer.

Volunteers will be instructed to press a button as soon as they feel a change in temperature. The final threshold will be defined by averaging the three consecutive tests. The three different diffuse inhibitory pain control techniques are:

- Ischemia conditioning stimulus, performed using a cuff and cuff (device for measuring blood pressure); 2) Thermal conditioning stimulus, performed using the Quantitative Sensitivity Test machine (TSA -- Medoc), with cold thermal stimulus; 3) Cold Pressur conditioning stimulus, carried out by introducing the patient's hand into a basin with water and ice at a temperature of 0 ° C.
- Pupil Examination (PLR): you will do a test lasting about 20 minutes in which a camera phone will record the size of your pupil during this period while you will hear some sounds. The exam is painless and has no side effects.

3 – List of routine procedures and how they are performed:

If you agree to participate in this research, you will receive both types of treatment, but you will be able to receive an active treatment or placebo (with no effect). The placebo has no effect, and is used to study what happens to the patient who does not receive the proposed treatment. In this way, you can be drawn to receive one of the two treatments. The groups will be chosen by lot. If you have been drawn to the placebo group, at the end of the evaluation you can do the same procedure in the active group without a draw. Transcranial magnetic stimulation has been used worldwide for depression, being already approved and widely used in Brazil. The coil generates a magnetic field (which is barely noticeable) and this field is painlessly directed to your brain. This treatment usually does not cause any side effects, but you may experience headache and nausea for the first three days, which usually last for 3 days and go away on their own. During stimulation, you will be awake at all times, following everything that is done. The study will evaluate the efficacy of RMT using the theta-burst method in the treatment of major depressive disorder in the elderly. The antidepressant drugs you are using will be withdrawn for research. The treatment lasts 3 months, with the first 20 days being followed, after which the patient returns every 15 days, and then returns once a month. Each stimulation session will take place once a day continuously, until completing 20 days, except weekends and holidays. This session will last for around 10 minutes.

If you agree to participate in this study, blood samples will be collected by peripheral puncture of the forearm vein. You will also collect the CSF. To perform this exam, you must sit still and a sting will be made on your back with a clean (sterile) fine needle that will be thrown away afterwards. CSF will be removed for laboratory tests. The blood test will be collected on the first day and on the 6th week after the start of the study.

For the realization of cortical excitability, the same Transcranial Magnetic Stimulation machine will be used. You will need to sit in a specialized chair and receive magnetic stimuli on the scalp with an appropriate device. This will stimulate your hand, in which electrodes with gel will be placed on the skin (without the use of needles) that will measure how your hand behaves with this stimulation. This lasts for about 30 minutes. There is no use of needles, the test is painless. This exam will be carried out in three moments, on the first day, 6th week and on the 12th week after the beginning of the study.

In addition, you will use actigraphy, which consists of a watch-like device that will stay on your wrist for 4 weeks. There is no discomfort.

After starting the study, you will be reassessed on the following occasions: 1, 2, 4, 6, 8 and 12 weeks after the first stimulation session.

4 – Discomfort and risk expected in the procedures of items 2 and 3:

For blood collection processes you may experience pain, discomfort or hematoma when the blood is drawn. Regarding the collection of cerebrospinal fluid, you may experience headache when standing up, subjective skin sensations (eg, cold, heat, tingling, pressure, etc.), local pain and skin infection at the site of the bite, which usually does not bring important consequences and can be treated with medication for local use. The occurrence of deep infections (meningitis) is extremely rare and will be avoided by the use of sterile and disposable material, using all hygiene techniques for the examination. Thus, the incidence of these complications tends to be close to zero. For the Transcranial Magnetic Stimulation procedure, the placement of a fabric cap on the head for magnetic mapping, which does not bring pain, but can bring some discomfort. Headache is possible, but it is mild and

uncommon. There may be a sensation of muscle contraction in the limbs during the examination, but this is part of the procedure and is not uncomfortable. There is a very low risk of a seizure occurring, but with security protocols used, they are rare. Other side effects were not seen during this test, which has been used for more than 25 years by dozens of research centers.

5 – Benefits for the participant: the benefit will be the improvement of depression or some of its symptoms during treatment. It is possible, but not guaranteed, that patients with this disease may benefit from the results of this study in the future, as well as their families.

6 - Research duration: 48 months

7 - Guarantee of access: At any stage of the study, you will have access to the professionals responsible for the research to clarify any doubts. The main investigator is Dr. Orestes Forlenza who can be found at Rua Ovídio Pires de Campos, 785, São Paulo - SP. Telephone 2661-7267. If you have any concerns or doubts about the research ethics, please contact the Research Ethics Committee (CEP) - Rua Ovídio Pires de Campos, 225 - 5º andar - tel: (11) 2661-7585, (11) 2661-1548, (11) 2661-1549 - E-mail: cappesq.adm@hc.fm.usp.br

8 - The freedom to withdraw consent at any time and to stop participating in the study is guaranteed, without prejudice to the continuity of its treatment at the Institution.

9 - The right to confidentiality is guaranteed - The information obtained will be analyzed together with other patients, and the identification of no patient will not be disclosed.

10 - The right to be kept up to date on the partial results of the research, when in open studies, or results that are known to the researchers, is guaranteed.

11 - Expenses and compensation: there are no personal expenses for the participant at any stage of the study, including exams and consultations. There is no financial compensation related to your participation, however in case of any medical problems caused directly or indirectly by the research procedures, you will receive all the necessary medical care, by our

team at the Psychiatric Institute and / or Hospital das Clínicas. In case of damage resulting from these complications, you will be compensated according to the legislation in force. ”

12 - It is the researcher's commitment to use the data and material collected only for this research.

I believe I have been sufficiently informed about the information that I read or that was read to me, describing the study “TREATMENT OF DEPRESSION IN ELDERLY PEOPLE WITH REPETITIVE MAGNETIC STIMULATION BY THE THETA BURST METHOD: CLINICAL, RANDOMIZED, DOUBLE-BLIND METHOD”

I was sufficiently informed about the study “TREATMENT OF DEPRESSION IN ELDERLY PEOPLE WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION BY THE THETA BURST METHOD: CLINICAL, RANDOMIZED, DOUBLE-BLIND TEST”.

I discussed the above information with the Principal Investigator (Prof. Dr. Orestes Vicente Forlenza) or the person (s) he delegated (Dr. Leandro da Costa Lane Valiengo) about my decision to participate in this study. The objectives, procedures, potential discomforts and risks and guarantees were clear to me. I voluntarily agree to participate in this study, sign this consent form and receive a copy initialed by the researcher.

_____ Date____/____/____

Signature of patient / legal representative

_____ Date____/____/____

Witness signature

For cases of patients under 18 years old, illiterate, semi-illiterate or with hearing or visual impairment. (FOR THE PROJECT RESPONSIBLE ONLY) I declare that I have appropriately and voluntarily obtained the Free and Informed Consent of this patient or legal representative to participate in this study.

_____ Date ____/____/____

Signature of the person responsible for the study

IDENTIFICATION DATA (OR INSTITUTIONAL IDENTIFICATION LABEL) OF THE RESEARCH PARTICIPANT OR LEGAL RESPONSIBLE

1. NAME:_____

IDENTITY DOCUMENT No.: _____

SEX: M □ F □ DATE OF BIRTH: _ / _ / _

ADDRESS:_____Nº:_____APT:_____

NEIGHBORHOOD:_____CITY:_____

CEP:_____PHONE: (___) _____

2. LEGAL RESPONSIBLE: _____

NATURE (degree of kinship, tutor, healer, etc.): _____

IDENTITY DOCUMENT: _____

SEX: M □ F □ DATE OF BIRTH: _ / _ / _

ADDRESS:_____Nº:_____APT:_____

NEIGHBORHOOD:_____CITY:_____

CEP:_____PHONE: (___) _____